REMARKS/ARGUMENTS

Upon entry of the amendments, claims 1-32 will be pending in the above-identified application. Claims 1, 13-18, and 27-32 have been amended. Applicants submit that the amendments are supported throughout the specification as originally filed as discussed below, and therefore, no new matter is added by these amendments.

Rejections under 35 U.S.C. § 112:

Claims 1-9, 13-20, and 27-32 stand rejected under 35 U.S.C. § 112, first paragraph because the Examiner alleges that the specification, while being enabling for: 1) a method for producing an anti-cancer immune response in an individual with a cancer, and 2) a composition comprising dendritic cells treated with BCG and interferon gamma, for administering into a cancer tissue, cancer bed, tissue area surrounding the cancer tissue, into a lymph node directly draining into a cancer area, or directly to a circulatory vessel duct that delivers blood or lymph to the cancer or a cancer afflicted organ, or into the circulatory system such that the cells are delivered to the cancer or cancer afflicted organ, wherein said dendritic cells can take up and process antigen and are enabled to induce an anti-cancer immune response subsequent to administration to the cancer tissue, does not reasonably provide enablement for: 1) a method for producing an anti-"tumor" immune response in an individual with a "tumor", and 2) a composition comprising dendritic cells treated with BCG and interferon gamma, for administering into the "tumor", "tumor" bed, tissue area surrounding the "tumor" tissue, into a lymph node directly draining into a "tumor" area, or directly to a circulatory vessel duct that delivers blood or lymph to the "tumor" or a "tumor" afflicted organ, or into the circulatory system such that the cells are delivered to the "tumor" or "tumor" afflicted organ, wherein said dendritic cells can take up and process antigen and are enabled to induce an anticancer immune response subsequent to administration to the "tumor" tissue. The Examiner asserts that the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. According to the Examiner, a tumor encompasses any enlargement or abnormal growth, which is

not necessarily cancerous, citing Stedman's Medical Dictionary, 25th ed., 1990, pages 1652-1653). The Examiner believes that it is not clear how one can successfully assess cancer therapy, wherein the cells to be assessed are tumor cells, which are not necessarily cancerous, and are unrelated to cancer, and thus having different etiology and characteristics, and would not predictably respond to cancer therapy. In view of the above, the Examiner alleges that it would be undue experimentation for one of skill in the art to practice the claimed invention as broadly claimed.

Although Applicant respectfully disagrees with the rejections and do not acquiesce to any reasoning provided by the Examiner, claims 1, 13-18, and 27-32 have been amended to further clarify the invention and to further expedite prosecution of the present invention. Claims 1, 13-18, and 27-32 have been amended to recite a "cancerous tumor." Support for these amendments can be found, for example, in the specification as filed in Example 2 on page 16, lines 16-19. Claims 2-9, 19 and 20 are dependent on a rejected base claim. As a claim upon which any of claims 2-9, 19 and 20 depend has been amended as set forth above, the claims are also believed to be free of the rejection. For the reasons set forth above, Applicant respectfully requests that the rejections under 35 U.S.C. § 112, first paragraph be withdrawn.

Rejections under 35 U.S.C. § 102:

Claims 1, 2, and 5 stand rejected under 35 U.S.C. § 102(b) as being anticipated by Labeur *et al.*, *J. Immunol.* 162:168-175, 1999. The Examiner believes that in claim 1, the ability to take up and process antigen does not have to be subsequent to administration to the individual. The Examiner further alleges that *Labeur et al.* teach that different culture conditions produce dendritic cells (DCs) with different degrees of maturation, and capacity to present antigen after incubation with the antigen citing to the abstract; page 168, second column, second and third paragraphs, bridging to page 169; page 171, second column, paragraph under Allostimulatory activity and presentation of OVA peptide; and Figure 3 on page 172. The Examiner believes that the ability to present antigen after being exposed to the antigen is the same as the ability to

uptake and process antigen. According to the Examiner, Labeur *et al.* teach that administration of the DCs induce protective tumor immunity in mice citing to page 172, and Figure 5 on page 174. The Examiner alleges that the method taught by Labeur *et al.* is the same as the claimed method, using the same dendritic cells, which can take up and process antigen, and induce an anti-tumor immune response when administered into an individual, and which are not terminally differentiated mature citing Labeur *et al.*, page 2 last line and bridging to page 3.

Applicants respectfully disagree with the rejections and do not acquiesce to any reasoning provided by the Examiner. Applicants submit that the presently claimed invention is generally directed towards a method of using dendritic cells that have been partially matured *in vitro* without exposure to antigen and to compositions comprising the partially matured dendritic cells formulated for administration to the individual. The partially matured dendritic cells are produced by exposure to maturation agents such as, for example, BCG. The partially matured dendritic cells are not exposed to antigen prior to administration thereby providing to an individual partially matured dendritic cells that can take up and process antigen *in vivo* and which are enabled to induce an anti-tumor immune response. Applicants respectfully submit that the cited reference alone does not teach each and every element of the presently claimed invention.

Labeur *et al.* fail to teach numerous aspects of the currently claimed invention. For example, rather than teaching administration of partially matured cells that have not been exposed to antigen, the cited reference teaches the administration of dendritic cells that have been exposed to tumor. The Examiner has cited to page 172 and Figure 5 as supporting her allegation. Contrary to the Examiner's assertions, page 172 and Figure 5 disclose the administration of i) bone marrow derived dendritic cells that have been produced by exposure to certain differentiation protocols and exposed to a tumor antigen, ii) tumor antigen alone, or iii) bone marrow dendritic cells alone. At page 172, left column, last line bridging to the right column, the authors report that the control groups were not protected against tumor growth. Thus, the cited reference does not teach the claimed method for administering partially matured

dendritic cells. For the reasons set forth above, Applicants respectfully request that the rejections under 35 U.S.C. § 102(b) be withdrawn.

Rejections under 35 U.S.C. § 103:

Claims 2-4 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Labeur *et al.*, *J. Immunol.* 162:168-175, 1999, in view of Murphy *et al.*, US 5,788,963. The teachings of Labeur *et al.* as alleged by the Examiner have been set forth above. The Examiner admits that Labeur *et al.* do not teach that: 1) DCs are obtained from skin, spleen, thymus, lymph nodes, umbilical cord blood, or peripheral blood, and 2) DCs are obtained from the individual to be treated or from a healthy individual HLA-matched to the individual to be treated. According to the Examiner, Murphy *et al.* teach the isolation of DCs for prostate cancer therapy, where the DCs are obtained from any tissue where they reside, including the skin, the spleen, bone marrow, lymph nodes and thymus as well as the circulatory system, including blood and lymph citing to column 5, lines 54-65. The Examiner asserts that Murphy *et al.* teach that human peripheral blood is an easily accessible ready source of human DCs and that cord blood is another source of human DCs. The Examiner further alleges that Murphy *et al.* teach that DCs can be obtained from a prostate cancer patient to be treated, or from a healthy individual with matched HLA antigens, because patients previously treated with radiation or chemotherapy often are not able to provide sufficient or efficient DCs. The Examiner believes that Murphy *et al.* also teach that $CD8^+$ T cells, after interaction with antigen presenting cells, which express MHC class I or II molecule associated with the antigen, are sensitized and capable of killing any cells that express the specific antigen associated with matching MHC class I molecule. The Examiner has noted that DCs are antigen presenting cells.

According to the Examiner, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to obtain the DCs taught by Labeur *et al.* from skin, spleen, bone marrow, thymus, lymph nodes, umbilical cord blood, or peripheral blood as taught by Murphy *et al.* to increase the number of available sources for making DCs. The Examiner believes that it would have been obvious that the DCs taught by Labeur *et al.* have

been isolated from the individual to be treated, as suggested by Murphy *et al.* to avoid unwanted rejection of foreign DCs. The Examiner further believes that it would have been obvious that the DCs taught by Labeur *et al.* have been isolated from a healthy individual HLA-matched to the individual to be treated as taught by Murphy *et al.* to increase the number of available DCs, for example, in situations where the patient to be treated cannot provide sufficient DCs, as taught by Murphy *et al.* In addition, the Examiner alleges that HLA-matched DCs would be necessary because antigen presentation of DCs is restricted to the complementing HLA molecule, in view of the teaching of Murphy *et al.*

Applicant respectfully disagrees with the above rejections. In particular, as set forth above with respect to the rejections of claim 1, Labeur *et al.* does not teach each and every element of the presently claimed invention. The DCs taught in Labeur *et al.* are not the same as the DCs used in the presently claimed methods. As such, Applicant submits that Labeur *et al.* when combined with Murphy *et al.* does not teach or suggest the invention encompassed by either claim 1 or dependent claims 2-4. As above, the DCs of Labeur *et al.* are contacted with antigen prior to administration to an individual to be treated. In the methods of the present invention, the immature dendritic cells, regardless of their source, are contacted with a dendritic cell maturation agent and prior to full maturation are administered to the patient. Contact with antigen takes place *in vivo* not *in vitro* as taught by Labeur *et al.* Murphy *et al.* does not teach the missing element of the claimed methods. Murphy *et al.* may teach various sources for dendritic cell precursors and methods for *in vitro* contacting the dendritic cells with a prostate cancer antigen, but there is no teaching or suggestion for administering partially matured dendritic cells that have not been contacted with a prostate tumor antigen. As such, Labeur *et al.* or Murphy *et al.* whether considered alone or in any combination do not teach or suggest the methods claimed. Accordingly, Applicant respectfully requests that the rejection of claims 2-4 under 35 U.S.C. § 103(a) be reconsidered and withdrawn.

Claims 6-9 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Labeur *et al.*, *supra*, in view of US 20050059151 (Bosch *et al.* priority US 60/317592, filed on September 6, 2001), and Chakraborty *et al.*, *Clin. Immunol.* 94:88-98, 2000). The alleged

teachings of Labeur *et al.* have been set forth above. The Examiner asserts that Labeur *et al.* further teach that the ability of DCs matured with CD40L to promote antitumor immunity correlates with their high efficiency of stimulating resting T cells and high production of IL-12 citing to page 173, second column, second paragraph. In addition, the Examiner alleges that Labeur *et al.* teach that although they do not know yet whether the high efficiency of stimulating resting T cells and high production of IL-12 are responsible for their potent *in vivo* immunostimulatory capacity, they speculate that the IL-12 production by DCs is critical for their *in vivo* function, since in other systems IL-12 is shown to generate a polarization to the immune response toward the Th1 pathway *in vivo*. In addition, the Examiner alleges that Labeur *et al.* teach that IL-12 is also a potent inducer of IFN-γ and TNF-α production by both NK cells and T cells, which cytokines are critically involved in the development of immune response citing to page 173, second column, second paragraph. Further, the Examiner has alleged that Labeur *et al.* teach the subcutaneous injection of 2×10^4 pulsed DCs into naïve recipient mice citing to page 170, first column, second paragraph. The Examiner asserts that the amount of DCs taught by Labeur *et al.* are within the range of the claimed amounts of DCs in claim 23. The Examiner notes that although Labeur *et al.* teach the use of TNF-α, LPS and CD40L for maturing DCs (page 4, first paragraph), Labeur *et al.* do not teach the use of BCG and IFN-γ for maturing CDs. Further, the Examiner notes that Labeur *et al.* do not teach: 1) BCG comprises whole BCG, cell wall constituents of BCG, BCG-derived lipoarabidomannans, or BCG components, 2) the BCG is heat- inactivated BCG or formalin-treated BCG, and 3) the effective amount of BCG is about 10^5 to 10^7 cfu per milliliter of tissue culture media and the effective amount of IFN-γ is about 100 to about 1000 Units per milliliter of tissue culture media.

The Examiner alleges that Bosch *et al.* teach that maturing the immature DCs with IFN-γ and BCG promotes DC production of IL-12, and reduces or inhibits production of IL-10, thereby priming the mature dendritic cells for a type 1 (Th-1) response citing to paragraph 0039. In addition, the Examiner alleges that Bosch *et al.* teach that in contrast to a type 1 response, a type 2 response is characterized by production of more IL-10 than IL-12 and lack of induction of a CTL response citing to paragraph 0022 the last two lines. The Examiner further

alleges that Bosch *et al.* teach that: 1) effective amounts of BCG typically range from about 10^5 to 10^7 cfu per milliliter of tissue culture media, 2) Effective amounts of IFN-γ typically range from about 100-1000 U per milliliter of tissue culture media (paragraph 0038). The Examiner asserts that Bosch *et al.* teach that BCG is an avirulent strain of *M. bovis*, and as used herein, BCG refers to whole BCG as well as cell wall constituents, BCG-derived lipoarabidomannans, and other BCG components that are associated with induction of a type 2 immune response (paragraph 0038), and that Bosch *et al.* teach that BCG is optionally inactivated, such as heat-inactivated BCG, formalin-treated BCG, and the like citing to paragraph 0038. According to the Examiner, because the type of BCG, and the amount of BCG and IFN-γ are the same as those of the claimed invention, Bosch *et al.* teach that maturation of dendritic cells can be monitored by methods known in the art, such as detection of cell surface markers or cytokine production (paragraph 0041).

As to Chakraborty *et al.*, the Examiner asserts that the reference teaches that DCs that produce IL-12 efficiently stimulate T cells, whereas DCs that produce IL-10 are inhibitory (abstract and Figure 2 on page 93) and that DCs that produce IL-12 up-regulate the co-stimulatory CD80 and CD86 (page 91, second column, first paragraph and Table 3 on page 95).

According to the Examiner, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to replace CD40L or LPS taught by Labeur *et al.* with BCG and IFN-γ, as taught by Bosch *et al.* in the method taught by Labeur *et al.* for maturing DCs for use in producing an anti-cancer response, because: 1) a combination of BCG and IFN-γ selectively produces more maturing DCs that secrete IL-12 than those inhibiting DCs secreting IL-10, as taught by Bosch *et al.*, 2) DCs that secrete IL-12 efficiently stimulate T cells, whereas DCs that produce IL-10 are inhibitory, as taught by Chakraborty *et al.*, and 3) the ability of DCs to promote antitumor immunity correlates with their high efficiency of stimulating resting T cells and high production of IL-12, as taught by Labeur *et al.* The Examiner notes that in other words, BCG and IFN-γ as maturing agent as taught by Bosch *et al.* would be advantageous, because they selectively enhance the production of stimulating DCs that secrete

IL-12, and therefore efficiently stimulating T cells, in view of the teaching of Chakraborty *et al* and promoting anti-tumor immunity, in view of the teaching of Labeur *et al.*

Applicant respectfully disagrees with the above rejections. In particular, as set forth above, Labeur *et al.* does not teach each and every element of the presently claimed invention. In particular, the DCs taught by Labeur *et al.* are not the same as the DCs in the presently claimed invention. The DCs taught by Labeur *et al.* are contacted with tumor antigen prior to administration while those of the present invention are not. Further, Applicant submits that Bosch *et al.* and/or Chakraborty *et al.* do not disclose or suggest any element missing from the teachings of Labeur *et al.* to render obvious any of claims 1 and 6-9. Even if either Basch *et al.* and/or Chakrabory *et al.* were to teach or suggest those elements alleged by the Examiner above, any combination of those references with Labeur *et al.* would not result in the present invention. If the references were combined as suggested by the Examiner, at most, the skilled artisan might use a maturation agent suggested by Bosch *et al.* to mature DCs that had been exposed to antigen prior to administration to a subject. That is not the invention as recited in any of claims 6-9. The addition of Chakrabory *et al.* which is alleged by the Examiner to teach the secretion of IL-12 by certain DCs provides nothing that would disclose or suggest the present invention. As such, Labeur *et al.* when considered alone or in any combination with Bosch *et al.* and/or Chakrabory *et al.* do not disclose or suggest the invention as recited in claims 6-9. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Claims 13-18 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Labeur *et al.*, *supra*. Certain teachings of Labeur *et al.* as set forth by the Examiner are above. The Examiner further asserts that Labeur *et al.* teach that subcutaneous injection is not the optimal cell delivery system for *in vitro* generated DCs, at least in the mice, because DCs migrate very inefficiently into the regional lymph nodes after subcutaneous injection into mice (page171, second column, last paragraph, bridging to page 172 and page174, second column, last paragraph). The Examiner notes that Labeur *et al.* do not teach DCs that are administered directly into the tumor, to a tissue area surrounding the tumor, into a lymph node directly

draining a tumor area, directly to a circulatory vessel duct that delivers blood or lymph to the tumor or a tumor afflicted organ, or into the circulatory system such that the cells are delivered to the tumor or tumor afflicted organ. According to the Examiner, it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to replace subcutaneous injection of the DCs taught by Labeur *et al.* with administration of the DCs directly into the tumor, to a tissue area surrounding the tumor, into a lymph node directly draining a tumor area, directly to a circulatory vessel duct that delivers blood or lymph to the tumor or a tumor afflicted organ, or into the circulatory system such that the cells are delivered to the tumor or tumor afflicted organ, because subcutaneous injection is not the optimal cell delivery system for *in vitro* generated DCs, at least in the mice as taught by Labeur *et al.*

Applicant respectfully disagrees with the above rejection. In particular, Applicant believes that the Examiner has failed to provide a proper rejection for *prima facie* obvious in that no basis for the rejection is provide. The Examiner has merely asserted that the claims are obvious because the cited reference teaches that another method is not optimal. No basis is provided why the claimed method would be an obvious substitution for subcutaneous injection. In addition, in order to further expedite prosecution Applicant also notes that as set forth above, Labeur *et al.* does not teach each and every element of the presently claimed invention. In particular, the DCs taught by Labeur *et al.* are contacted with tumor antigen prior to administration and are therefore not the same as the DCs in the presently claimed invention. As such, contrary to the Examiners assertions, it would not have been obvious to one of ordinary skill to choose direct administration of the presently claimed DCs over subcutaneous injection. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Claims 19 and 20 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Labeur *et al.*, *supra*, in view of Nikitina *et al.*, *Int. J. Cancer* 94:825-833, 2001. The Examiner admits that Labeur *et al.* do not teach that DCs are administered as an adjuvant to radiation therapy, chemotherapy, or combinations thereof and that Labeur *et al* do not teach that the partially matured dendritic cells are administered prior to, simultaneous with, or subsequent

to radiation therapy, chemotherapy, or combinations thereof. But according to the Examiner, Nikitina *et al.* teach that gamma irradiation induces the dramatic ability of DCs injected intravenously (i.v.) or subcutaneously (s.c.) to migrate and penetrate cancer tissue, and to take up apoptotic bodies, resulting in enhanced, potent antitumor response citing to the abstract and to page 831, second column, last paragraph and bridging to page 382). The Examiner alleges that it would have been *prima facie* obvious for one of ordinary skill in the art at the time the invention was made to combine DCs administration taught by Labeur *et al.* with radiation therapy, because gamma irradiation induces the dramatic ability of DCs injected i.v. or s.c. to migrate and penetrate cancer tissue, and to take up apoptotic bodies, resulting in enhanced, potent antitumor response, as taught by Nikitina *et al.*

Applicant respectfully disagrees with the rejection of claims 19 and 20. As set forth above, Labeur *et al.* does not teach the methods of the presently claimed invention. In particular, the DCs taught in Labeur *et al.* are exposed to antigen *in vitro* prior to administration to an individual and are not the same as the DCs used in the presently claimed invention. Thus, Applicant submits that Labeur *et al.* even if combined with Nikitina *et al.* fail to teach or suggest each and every element of claims 19 and 20. If the DCs of Labeur *et al.* were combined with the methods of Nikitina *et al.* the dendritic cells would be exposed to a tumor antigen *in vitro* prior to administration to a patient that had received radiation therapy. This is not the invention of claims 19 and 20. Accordingly, Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) be withdrawn.

Claims 21-23 and 27-32 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.*, *Cancer* 89: 2646-54, 2000, in view of Sukhatme *et al.* (US 6,797,488), and as evidenced by Labeur *et al.*, *supra*, or in the alternative, over Labeur *et al.*, *supra*, in view of US 20050059151, *supra*, and Chakraborty *et al.*, *supra*, as applied to claims 6-9 above, and further in view of Sukhatme *et al.* (US 6,797,488). According to the Examiner, claims 21 and 27-32 recite the claimed composition for administering: 1) *in vivo*, directly into the tumor, 2) into a tumor bed subsequent to surgical removal or resection of the tumor, 3) to an tissue area surrounding the tumor, 4) into a lymph node directly draining a tumor area, 5) to a

circulatory vessel duct that delivers blood or lymph to the tumor, tumor bed, or a tumor afflicted organ, or 6) into the circulatory system such that the cells are delivered to the tumor, tumor bed, or tumor afflicted organ. The Examiner alleges that this limitation is viewed as a recitation of intended use and therefore is not given patentable weight in comparing the claims with the prior art. The Examiner asserts that claims 21 and 27-32 read on the ingredient *per se*, which is a composition comprising dendritic cells partially matured *in vitro*. The Examiner asserts that Triozzi *et al.* teach that DCs generated *in vitro* by GM-CSF and IL-4 express the costimulatory molecules CD80 and CD86, and a low number of CD83 (page 2649, first column, under Results). The Examiner further asserts that Triozzi *et al.* teach that the amount of DCs generated is from 8.0×10^7 to 18×10^7 (page 2649, first column, under Results), which is within the range of the claimed amount of DCs, as claimed in claim 23. The Examiner alleges that Triozzi *et al* do not teach DCs in a pharmaceutically acceptable carrier. But the Examiner further asserts that Sukhatme *et al.* (US 6,797,488) teach an anti-angiogenic protein, fusion protein thereof (column 2, item under Summary of the Invention, bridging column 3), and a composition thereof, wherein the protein is combined with a pharmaceutically acceptable carrier (column 16, last paragraph, bridging column 17).

The Examiner further alleges that the DCs generated by GM-CSF and IL-4 taught by Triozzi *et al.* would retain the ability to uptake and process antigen, as evidenced by Labeur *et al.* The Examiner asserts that Labeur *et al.* teach that DCs generated from GM-CSF and IL-4, with or without the addition of TNF-alpha, exhibit intermediate ability to present antigen, after being exposed to the antigen (page 8, last paragraph and bridging to page 9 and Figure 3 on page 9), which is the same as the claimed ability to uptake and process antigen. The Examiner believes that although the Triozzi reference does not explicitly teach that the generated DCs are partially mature, and retain the ability to uptake and process antigen, however, the claimed DCs appear to be the same as the prior art DCs, absent a showing of unobvious differences. The Examiner has noted that the Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product and that in the

absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. The Examiner believes that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the DCs taught by Triozzi *et al.* with a pharmaceutically acceptable carrier, as taught by Sukhatme *et al.* for their storage.

Applicant respectfully disagrees with the rejection of claims 21-23 and 27-32 as set forth above by the Examiner. The dendritic cells of the present invention are not the same as those of the present invention. In particular, the dendritic cells of Triozzi *et al.* are immature dendritic cells and are not partially matured dendritic cells as set forth in claims 21-23 and 27-32. As set forth in the specification at page 9, line 28 through page 10, line 7 and page 11, lines 5 through 30, immature dendritic cells and partially mature dendritic cells differ in a number of ways including the levels of expression of a number of cell surface antigens, CD14, CD11c, CD80 and CD86, and in the phosphorylation level of a number of intracellular proteins including for example, jak2. The specification also demonstrates differences between monocytes cultured in GM-CSF and IL-4 and those induced to mature in Example 1 of the specification as filed. As such, the dendritic cells of Triozzi *et al.* are not the same as those recited in claims 21-23 and 27-32.

Further, as the dendritic cells of claims 21-23 and 27-32 are not the same as those taught by Triozzi *et al.* in view of Labeur *et al.*, the addition of Sukhatme *et al.* does nothing to teach or suggest the claimed invention. The Examiner has cited Sukhatme *et al.* as disclosing a pharmaceutical carrier. Addition of this teaching with those of Triozzi *et al.* in view of Labeur *et al.* does not disclose or suggest the present invention.

The Examiner has also asserted that alternatively, with regards to claims 21-23 and 27-32, the teachings of Labeur *et al.*, Bosch *et al.* and Chakraborty *et al.* as set forth above when combined with the teachings of a pharmaceutically acceptable carrier render obvious the invention. According to the Examiner, one would have expected that the non-terminally matured DCs taught by the combined art would up-regulate the co-stimulatory molecules CD80 and

CD86, because one would have expected that the DCs are those that secrete IL-12, and because up-regulation CD80 and CD86 is the property of DCs that secrete IL-12, as taught by Chakraborty *et al.* The Examiner further alleges that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the DCs taught by Labeur *et al.*, Bosch *et al.* and Chakraborty *et al.* with a pharmaceutically acceptable carrier, as taught by Sukhatme *et al.* for their storage.

Applicant respectfully disagrees with the rejection of claims 21-23 and 27-32 as set forth by the Examiner. In particular, as set forth above, Labeur *et al.* does not teach the DCs of the present invention. The DCs taught in Labeur *et al.* are contacted with tumor antigen prior to administration. Thus, Applicant submits that Labeur *et al.* cannot be combined with Bosch *et al.* and Chakraborty *et al.* to teach or suggest the invention as set forth in claims 21-23 and 27-32. In addition, Applicant respectfully submits that contrary to the Examiner's assertions one of ordinary skill would not have expected non-terminally matured DCs to up-regulate CD80 and CD86. For example, Chakraborty *et al.* teach that culturing plastic-adherent circulating monocytes in GM-CSF and IL-4 followed by further maturation in interferon-gamma plus bacterial superantigens can give rise to two diametrically opposite types of DCs - one stimulatory and another inhibitory. See page 88, col. 1. Only the stimulatory cells were shown to synthesize IL-12 and expression of higher amounts of costimulatory molecules. As taught by Chakraborty *et al.*, one of skill in the art could instead have expected inhibitory DCs that did not upregulate CD80 and CD86, for example. Moreover, the DCs taught by Chakraborty *et al.* are mature and not non-terminally matured DCs as alleged by the Examiner. For the reasons set forth above, one of ordinary in the art at the time of invention could not have nor would have been motivated to combine the references as suggested by the Examiner. Accordingly, Applicant respectfully requests that the rejection of claims 21-23 and 27-32 under 35 U.S.C. § 103(*a*) be withdrawn.

Claim 24 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.*, *supra*, in view of Sukhatme *et al.*, *supra*, and as evidenced by Labeur *et al.*, *supra*, as applied for claim 21, and further in view of Murphy *et al.* (US 5,788,963), or in the alternative, over Labeur *et al.*, *supra*, in view of US 20050059151 (Bosch *et al.*, *supra*), and

Chakraborty *et al.*, *supra*), as applied to claim 21, and further in view of Murphy *et al.* (US 5,788,963). The Examiner notes that the teachings of Triozzi *et al.*, Sukhatme *et al.*, and Labeur *et al.* have been set forth above and that the references do not teach cryopreservation of the DCs subsequent to their partial maturation, *i.e* , after their generation from exposure to GM-CSF and IL-4. The Examiner alleges that Murphy *et al.* teach cryopreservation of DCs (columns 7-8, and Example 7 on columns 16-18). According to the Examiner, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to cryopreserve the generated DCs taught by Triozzi *et al.*, Sukhatme *et al.*, and Labeur *et al.* using the method taught by Murphy *et al.* for extended use of the generated DCs.

Applicants respectfully disagree with the rejection of claim 24 as set forth the Examiner. As above regarding claim 21, the DCs taught by Triozzi *et al.* are immature dendritic cells and are not the same as the partially mature dendritic cells of the present invention. Further, as set forth above, the combination of Sukhatme *et al.* does not suggest or disclose the composition of claim 21. Therefore, any combination of Triozzi *et al.*, Sukhatme *et al.*, in view of Labeur *et al.* with Murphy *et al.*, alleged to teach cryopreservation of dendritic cells, do not teach or suggest each and every element of independent dependent claim 24.

Alternatively, with regards to claim 24, the Examiner notes that the teaching of Labeur *et al.*, Bosch *et al.* and Chakraborty *et al.* has been set forth above and that the references do not teach cryopreservation of the DCs subsequent to their partial maturation, *i.e.*, after their generation. As above, the Examiner alleges that Murphy *et al.* teach cryopreservation of DCs. According to the Examiner, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to cryopreserve the generated DCs taught by Labeur *et al* , Bosch *et al.* and Chakraborty *et al.* using the method taught by Murphy *et al.* for extended use of the generated DCs.

Applicant respectfully disagrees with the rejection of claim 24 as set forth by the Examiner. As set forth above, Labeur *et al.* does not teach or disclose the partially matured dendritic cells of the presently claimed invention. Thus, Applicant submits that Labeur *et al.*

even if combined with Bosch *et al.*, Chakraborty *et al.*, and Murphy *et al.* fail to teach or suggest each and every element of claim 24. As such, the Examiner is requested to reconsider and withdraw the rejection of claim 24 under 35 U.S.C. § 103(a).

Claims 25 and 26 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Triozzi *et al.*, *supra*, in view of Sukhatme *et al.*, *supra*, and as evidenced by Labeur *et al.*, *supra*, as applied for claim 21, and further in view of Murphy *et al.* (US 5,788,963), or in the alternative, over Labeur *et al.*, *supra*, in view of US 20050059151 (Bosch *et al.*, *supra*), and Chakraborty *et al.*, *supra*, as applied to claim 21, and further in view of Murphy *et al.* (US 5,788,963). The teachings of each of the cited references as alleged by the Examiner has been set forth above. In regard to this rejection, the Examiner has alleged that it would have been obvious that the DCs taught by Triozzi *et al.*, Sukhatme *et al.*, and Labeur *et al.* have been isolated from the individual to be treated, as suggested by Murphy *et al.*, to avoid unwanted rejection of foreign DCs. The Examiner further alleges that it would have been obvious that the DCs taught by Triozzi *et al.*, Sukhatme *et al.*, and Labeur *et al.* have been isolated from a healthy individual HLA matched to the individual to be treated as taught by Murphy *et al.* to increase the number of available DCs, for example, in situations where the patient to be treated cannot provide sufficient DCs, as taught by Murphy *et al.*

Applicant respectfully disagrees with the rejection of claims 25 and 26 as set forth by the Examiner. As set forth above regarding claim 21, the DCs taught by Triozzi *et al.* are not partially matured dendritic cells as recited in the present claims. As such, the teachings of Labeur *et al.* are not relevant to the teachings of Triozzi *et al.* Moreover, for reasons mentioned above, Triozzi *et al.*, Labeur *et al.*, Sukhatme *et al.* and Murphy *et al.* whether considered alone or in any combination fail to teach or suggest either independent claim 21 or its dependent claims, for example, claims 25 and 26.

Alternatively, the Examiner has rejected claims 25 and 26 noting that the teachings of Labeur *et al.*, Bosch *et al.* and Chakraborty *et al.* as set forth above do not teach that the generated DCs can be isolated from the individual to be treated or from a healthy individual

HLA-matched to the individual to be treated. But, the Examiner alleges that Murphy *et al.* teach that DCs can be obtained from a prostate cancer patient to be treated, or from a healthy individual with matched HLA in terms of HLA antigens, because patients previously treated radiation or chemotherapy often are not able to provide sufficient or efficient DC's. The Examiner also asserts that Murphy *et al.* teach that $CD8^+$ T cells, after interaction with antigen presenting cells, which express MHC class I or II molecule associated with the antigen, are sensitized and capable of killing any cells that express the specific antigen associated with matching MHC class I molecule. The Examiner has also noted that DCs are antigen presenting cells.

According to the Examiner, it would have been obvious that the DCs taught by Labeur *et al.*, Bosch *et al.* and Chakraborty *et al.* can be isolated from the individual to be treated, as suggested by Murphy *et al.* to avoid unwanted rejection of foreign DCs. The Examiner further alleges that it would have been obvious that the DCs taught by Labeur *et al.* Bosch *et al.* and Chakraborty *et al.* can be isolated from a healthy individual HLA-matched to the individual to be treated as taught by Murphy *et al.* to increase the number of available DCs, for example, in situations where the patient to be treated cannot provide sufficient DCs, as taught by Murphy *et al.* Still further, the Examiner alleges that HLA-matched DCs would be necessary, because antigen presentation of DCs is restricted to the complementing HLA molecule, in view of the teaching of Murphy *et al.*

Applicant respectfully disagrees with the rejections and do not acquiesce to any reasoning provided by the Examiner. As set forth above, Labeur *et al.* does not teach the partially mature dendritic cells of the presently claimed invention. Thus, Applicant submits that any combination of Labeur *et al.* with Bosch *et al.*, Chakraborty *et al.*, and Murphy *et al.* will not teach or suggest the invention as set forth in claims 25 and 26. In view of the above remarks Applicant respectfully requests the Examiner to reconsider and withdraw the rejection of claims 25 and 26 under 35 U.S.C. § 103(a).

CONCLUSION

In view of the foregoing, Applicant believes all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 206-467-9600.

Respectfully submitted,

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